Efficacy and safety of submucosal tunneling endoscopic resection for subepithelial tumors in the upper GI tract: a systematic review and meta-analysis of >2900 patients

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Background and aims: Submucosal tunnel endoscopic resection (STER) is an emerging therapeutic tool that allows direct visualization and resection of submucosal tunneling endoscopic resection (SETs) from the upper GI tract while maintaining the integrity of the mucosa. Our aim was to conduct a systematic review and meta-analysis to evaluate the efficacy and safety of STER in treating all types of SETs found in the upper GI tract.

Methods: A comprehensive search of major databases such as PubMed/Medline, Embase, *Cumulative Index to Nursing and Allied Health Literature*, Cochrane, Web of Science, and Google Scholar was conducted to identify studies that reported on STER. The primary outcomes were R0 resection, en bloc resection, and adverse events (AEs) of STER. Secondary analysis was performed for different regions of the upper GI tract, recurrence rate, and various adverse events.

Results: Eighteen studies with 2941 patients were included; the mean age was 49.74 years, and 61.82% were male. Pooled rates for the overall R0 resection, en bloc resection, and AEs were 92.4%, 91.5%, and 17.8%, respectively. However, only 1.2% of AEs were considered severe. The en bloc resection rate for the tumors in the esophagogastric junction layer was lower at 81.5%. The R0 and en bloc resection rates for tumors originating from the muscularis propria layer were also lower (88.3% and 89.1%). Gas-related adverse events were the most frequent AE with a rate of 5.9%. The recurrence rate was 2.3%.

Conclusions: Our meta-analysis showed that STER is overall an effective and safe therapeutic modality to remove SETs from the upper GI tract. (iGIE 2023;2:529-37.)

Submucosal tunneling endoscopic resection (SETs) are defined as protruding lesions in the GI tract that originate below the normal, overlying mucosa.[1] With advances in diagnostic technology, endoscopic techniques such as endoscopic submucosal dissection (ESD), EMR, endoscopic submucosal excavation, and submucosal tunneling endoscopic resection (STER) have emerged recently as therapeutic tools for the management of the SETs.[2] Although most SETs are benign, a study by Polkowski[3] in 2005 determined that approximately 13% of the upper GI SETs were malignant, and an additional 8% had malignant potential. The risk of malignancy also varies with the type, location, and size of the SET.

SETs have a broad differential diagnosis, which includes but is not limited to, leiomyomas, GI stromal tumors (GISTs), schwannomas, lipomas, and neurofibromas.[1] SETs smaller than 2 cm are usually asymptomatic and can often be managed by surveillance while larger SETs require aggressive treatment, including surgery and, in some cases, chemotherapy.[4] Currently, there is no consensus on the management of SETs based on histopathology results alone. For example, resection of leiomyomas is only recommended if they are large (>4 cm) or are symptomatic.[5] Conversely, the European Society for Medical Oncology recommends that all GISTs should be resected regardless of size and tumor; in practice, however, this recommendation is not strictly followed.[1] Although results of a needle biopsy may provide a histopathologic diagnosis, there is a risk for sampling error and delayed diagnosis of malignancy.[2] Periodic endoscopic surveillance is challenging because of patient compliance and cost-effectiveness issues.

Endoscopic techniques such as ESD and EMR provide a solution for the resection of neoplasia from the mucosal and superficial submucosal layers while maintaining the integrity of

the bowel wall.[6] However, not all lesions that arise from the deep submucosal layers or muscularis propria (MP) layer can be fully and safely removed with EMR or ESD. For such tumors, and those >4 cm, surgery is currently the primary treatment modality.

STER was first introduced in 2012 as an endoscopic technique for the removal of neoplasia from the submucosal and the MP layers while leaving the mucosa intact, and thus avoiding full-thickness resection.[6-8] This technique involves creating a longitudinal or transverse mucosal incision proximal to the lesion, followed by the creation of a submucosal tunnel.[6,9] This tunnel allows for access to the tumor, which is then enucleated and removed with the capsule intact. The tunnel is then irrigated, and the entry site is closed with clips after the procedure.[9] The benefit of maintaining the integrity of the GI tract mucosa and submucosa is that it promotes faster wound healing and leads to fewer postoperative GI tract leaks and bleeding adverse events compared with techniques that result in the disruption of the mucosal or submucosal integrity.[4] In recent years, multiple studies have shown that STER is an effective alternative therapy to surgery for SETs.[1,2,4,5,8-10]

We performed a systematic review and meta-analysis to evaluate the efficacy and safety of STER in the management of SETs of the upper GI tract.

METHODS

Search strategy

We performed a comprehensive literature search from 6 major databases (PubMed/Medline, Embase, *Cumulative Index to Nursing and Allied Health Literature*, Cochrane, Web of Science, and Google Scholar) using variations of the key words "STER," "submucosal tunneling endoscopic resection," "submucosal tumor," "upper gastrointestinal tract," "muscularis propria," "lesion," "esophagus," and "stomach" from inception to November 15, 2022. The initial literature search was independently performed by 2 authors (K.M.T. and B.S.D.) who reviewed the titles and abstracts of the studies. If there was any discrepancy in the article selection, the decision was arbitrated by a third author (G.N.). The full texts of the remaining articles were then retrieved for further review. The references of the selected articles were also reviewed to identify additional articles that could meet the inclusion criteria. The process is described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Fig. 1).

Eligibility criteria

Inclusion criteria were (1) use of STER for management of upper GI SETs; (2) adult patients (≥18 years old) of either sex; (3) adequate reporting of the patient data; (4) sample size of at least 20 patients; (5) full manuscripts; and (6) published in the English language. Furthermore, if there were multiple studies from the same authors and/or the same institutions, the locations and the study periods of each article were thoroughly reviewed to avoid duplicating the data to be included in the analysis.

Exclusion criteria were (1) case reports and case series; (2) studies with <20 patients; (3) laboratory science–based articles without patient data; (4) animal studies; (5) published in languages other than English; (6) studies with duplicate data; and (7) available only in abstracts.

Quality assessment

The Newcastle-Ottawa Scale was used to assess the methodologic quality of the observational cohort studies. Based on a star system representing 9 items, a study was categorized as low, moderate, or high quality if 0 to 3, 4 to 6, and 7 to 9 stars were allocated, respectively.[11] The methodologic quality of randomized controlled trials (RCTs) was evaluated with the Revised Cochrane risk-of-bias tool, which consists of 5 domains: randomization process, derivations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.[12] The risk of bias for an RCT was rated as high, low, or some concern based on the individual elements in the 5 domains. Quality appraisal for each study was performed by 2 authors (K.M.T. and L.H.). A third author (B.S.D.) arbitrated for any disagreement.

Study outcomes

The primary outcomes assessed were the rates of R0 resection, en bloc resection, and overall adverse events. The adverse events were further defined as mild, moderate, or severe per the American Society for Gastrointestinal Endoscopy (ASGE) lexicon.[13] The secondary outcomes were the rates of R0 resection and en bloc resection in the esophagus, stomach, esophagogastric junction (EGJ), and the MP layer; the rates of individual adverse events that include bleeding, infection or fever, perforation, gas-related adverse events without obvious perforation, and other adverse events; and the rate of recurrence. Perforation was defined as full-thickness resection with mucosal rupture that can present as presence of air or luminal contents outside the GI tract.[1,2,4,5,7-10] Gas-related adverse events without obvious perforation include but are not limited to pneumomediastinum, pneumothorax, subcutaneous emphysema, and pneumoperitoneum.

R0 resection was defined as the complete removal of the tumor with negative vertical and lateral margins, and en bloc resection was defined as the resection of the tumor in one nonfragmented piece with an intact capsule.[2,5,8,13,14] Recurrence was defined as a lesion arising within 1 cm of the resected area 6 months after STER.

Data analysis and heterogeneity

Using the random effects model with a 95% confidence interval (CI), we calculated the pooled estimates for each outcome of interest.[15] To preserve the integrity of the data and to avoid inadvertently adding bias to the outcomes, weighted summary statistics were calculated when values of

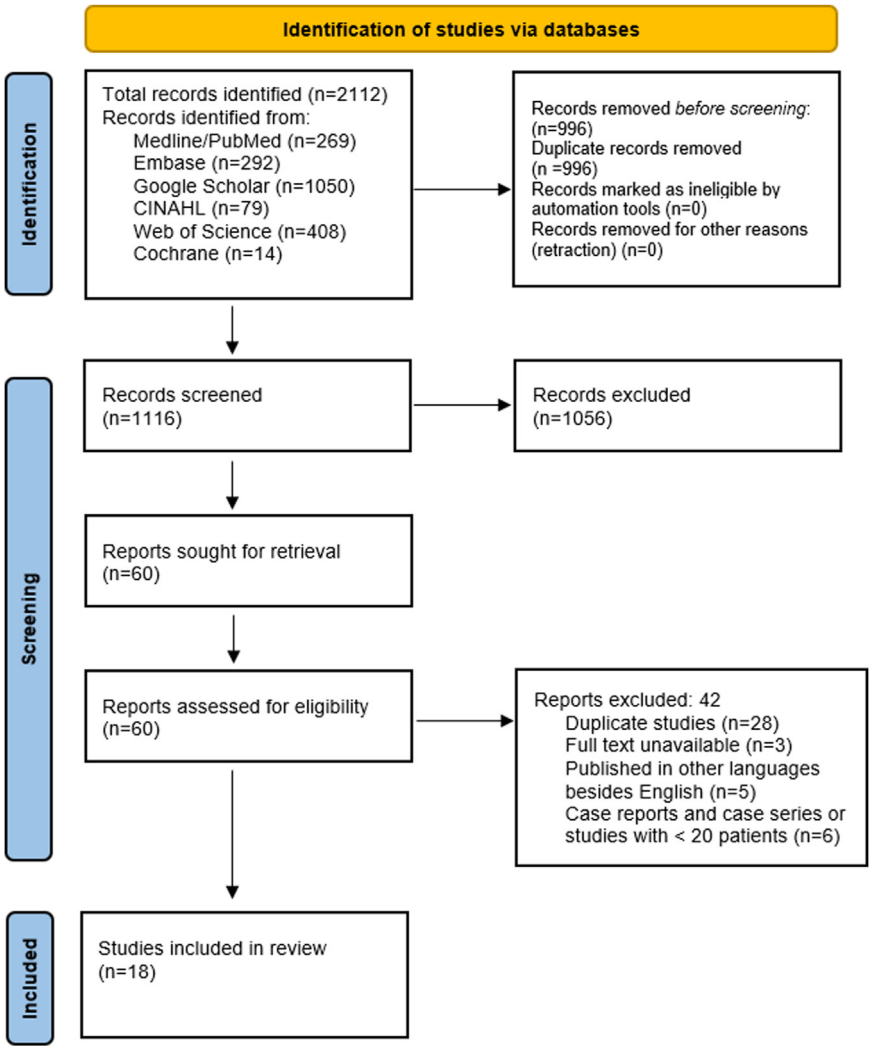

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for the study selection process.

zero occurred in the data. The Cochrane Q statistical test was used to assess the heterogeneity between study-specific estimates.[16,17] Values <30%, 30% to 60%, 61% to 75%, and >75% were suggestive of low, moderate, substantial, and considerable heterogeneity, respectively.[18] The Cochrane Q test was used for the calculation of 95% prediction intervals, which identify the dispersion of the effects.[19] Statistical analysis was performed by using Comprehensive Meta-Analysis software version 3.0 (Biostat, Englewood, NJ, USA).

Publication bias

Publication bias was assessed qualitatively by using funnel plots and quantitatively by using the Egger test.[20-22] If publication bias was present, the fail-safe N test and trim-and-fill test were used to assess the impact of the bias.[23] The impact was considered minimal if the reported data and the actual outcome were estimated to be equal; moderate if there was a change in the effect size but not in the final finding; and severe if the conclusion of the analysis was jeopardized by the bias.[24,25]

RESULTS

Study selection and characteristics of included studies

An initial search generated 2112 results, and 52 articles were initially determined to meet the inclusion criteria for the meta-analysis. During the review process, we identified several studies that had overlapping cohorts. Only the studies with the most suitable data were included in this analysis. After careful review, a total of 18 articles (15 retrospective cohort studies, 2 prospective cohort studies, and 1 RCT) were included in the final analysis.

A total of 2941 patients underwent STER for SETs; 61.82% (n = 1791) were male, and 38.18% (n = 1106) were female. The mean age was 49.74 ± 3.25 years. The average size of the lesions was 22.70 ± 6.40 mm. There were 2161 esophageal lesions, 179 gastric lesions, and 601 EGJ lesions. The majority of the gastric lesions (n = 130) were found in cardia, and there were 19 and 6 lesions in the fundus and corpus,

TABLE 1. Summary of studies included in the meta-analysis

Author	Type of study	Center	Mean age (y)	Total no. of patients	Male	Female
Xiu et al, 2019[1]	Retrospective cohort study	Single	53.4	43	21	22
Tan et al, 2016[5]	Retrospective cohort study	Single	51.3	20	8	12
Du et al, 2019[8]	Retrospective cohort study	Single	46.9	165	112	53
Lu et al, 2014[9]	Retrospective cohort study	Single	50.9	42	18	24
Li et al, 2018[14]	Retrospective cohort study	Single	46	47	33	14
Chen et al, 2020[15]	Retrospective cohort study	Single	52	90	59	31
Nabi et al, 2019[26]	Prospective cohort study	Single	44.68	44	23	21
Xu et al, 2019[27]	Retrospective cohort study	Single	52.05	40	22	18
Zhou et al, 2015[28]	Retrospective cohort study	Single	46.2	21	18	3
Xu et al, 2022[29]	Retrospective cohort study	Single	50	1701	1107	594
Ye et al, 2014[31]	Prospective cohort study	Single	48	85	47	38
Chen et al, 2022[32]	Retrospective cohort study	Single	48.8	72	22	50
Yang et al, 2022[33]	Retrospective cohort study	Single	50	42	28	14
Wang et al, 2022[35]	Retrospective cohort study	Single	55.5	44	NR	NR
Liu et al, 2022[36]	Randomized controlled trial	Single	51.58	136	75	61
Wu et al, 2021[38]	Retrospective cohort study	Single	54	242	131	111
Wang et al, 2015[39]	Retrospective cohort study	Single	44	80	49	31
Zhang et al, 2019[40]	Retrospective cohort study	Single	49.93	27	18	9

NR, Not reported.

respectively. There was 1 lesion each in the antrum and the pylorus. The region of 22 gastric lesions was not specified. An additional analysis was performed on 1237 lesions arising from the MP layer throughout the upper GI tract. The SETs could be further categorized as leiomyoma (n = 2600), GIST (n = 160), schwannoma (n = 46), lipoma (n = 19), and others (n = 123). All studies were conducted in China, except for Nabi et al,[26] which was performed in India.

Table 1 presents a summary of baseline demographic characteristics of the studies included in the systematic review and meta-analysis.

Quality assessment

Based on the quality assessment scales, 16 observational cohort studies were considered of moderate quality, and 1 cohort study was of low quality (Table 2). The RCT was determined to be of low risk of bias (Table 3).

Primary outcomes

The pooled rates for the following primary outcomes were estimated as follows: (1) overall R0 resection (Fig. 2): 92.4% (95% CI, 85.7-96.1; $I^2 = 81$; $P = .00$); (2) overall en bloc resection (Fig. 3): 91.5% (95% CI, 85.6-95.1; $I^2 = 89$; $P = .00$); and (3) overall adverse events (Fig. 4): 17.8% (95% CI, 13.0-23.9; $I^2 = 87$; $P = .00$).

On further subgroup analysis per the ASGE lexicon, the pooled rates for mild, moderate, and severe adverse events were 15.4% (95% CI, 10.7-21.5; $I^2 = 88$; $P = .00$), 3.4% (95% CI, 2.3-5.2; $I^2 = 43$; $P = .00$), and 1.2% (95% CI, .9-1.7; $I^2 = 0$; $P = .00$), respectively.

Secondary outcomes

R0 resection. The pooled rates for R0 resection of SETs from different regions of the upper GI tract are as follows: (1) esophageal lesions: 91.4% (95% CI, 82.3-96.0; $I^2 = 81$; $P = .00$); (2) lesions from the EGJ: 96.1% (95% CI, 72.6-99.6; $I^2 = 77$; $P = .005$); and (3) gastric lesions: 90.6% (95% CI, 57.8-98.5; $I^2 = 74$; $P = .023$).

En bloc resection. The pooled rates for en bloc resection of SETs from different regions of the upper GI tract are as follows: (1) esophageal lesions: 90.9% (95% CI, 83.8-95.1; $I^2 = 78$; $P = .00$); (2) lesions from the EGJ: 81.5% (95% CI, 68.1-90.1; $I^2 = 67$; $P = .00$); and (3) gastric lesions: 91.7% (95% CI, 74.5-97.7; $I^2 = 67$; $P = .00$).

Individual AEs

The pooled rates for individual adverse events were also analyzed. They are as follows: (1) bleeding: 2.3% (95% CI, 1.2-4.4; $I^2 = 72$; $P = .00$); (2) infection or fever: 3.3% (95% CI, 2.1-5.4; $I^2 = 62$; $P = .00$); (3) perforation: 2.8% (95% CI, 1.2-6.2; $I^2 = 85$; $P = .00$); (4) gas-related adverse events without evidence of obvious perforation: 5.9% (95% CI, 3.0-11.1; $I^2 = 85$; $P = .00$); and (5) other adverse events: 4.5% (95% CI, 2.8-7.0; $I^2 = 59$; $P = .00$).

TABLE 2. Quality assessment of the cohort studies with the Newcastle-Ottawa Scale

Author	Newcastle-Ottawa Scale		
	Selection	Comparability	Outcome
Xiu et al, 2019[1]	**	*	**
Tan et al, 2016[5]	***	*	**
Du et al, 2019[8]	***		**
Lu et al, 2014[9]	**	*	*
Li et al, 2018[14]	***		**
Chen et al, 2020[15]	***	*	**
Nabi et al, 2019[26]	**		**
Xu et al, 2019[27]	**	*	**
Zhou et al, 2015[28]	**		**
Xu et al, 2022[29]	**		*
Ye et al, 2014[31]	***		**
Chen et al, 2022[32]	**		**
Yang et al, 2022[33]	**	*	**
Wang et al, 2022[35]	**		**
Wu et al, 2021[38]	***		**
Wang et al, 2015[39]	***		**
Zhang et al, 2019[40]	**	*	**

The star indicates the Newcastle-Ottawa Scale system was explained under Quality Assessment in the Methods section. The maximum number of stars that can be allocated to selection, comparability, and outcome domains were 4, 2, and 3 stars, respectively. If a domain is blank, no star has been allocated.

TABLE 3. Quality assessment of the randomized controlled trial study with revised Cochrane risk-of-bias tool

	Randomization process	Deviations from the intended interventions	Missing outcome data	Measurement of outcome	Selection of the reported result	Overall
Liu et al, 2022[36]	+	+	+	!	+	+

+ represents low risk of bias; ! represents some concerns for bias; - represents high risk of bias.

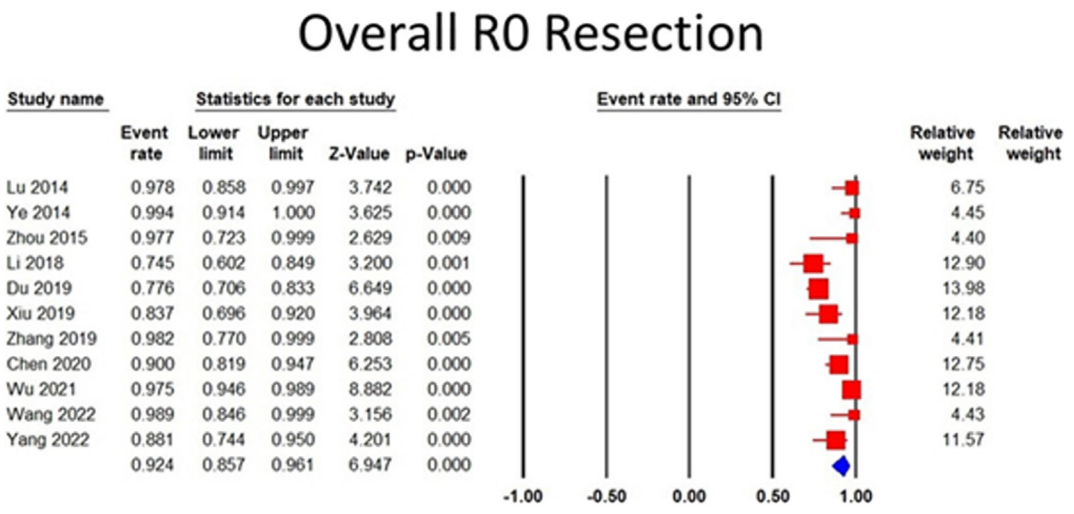

Figure 2. Forest plot for the pooled rate of overall R0 resection.

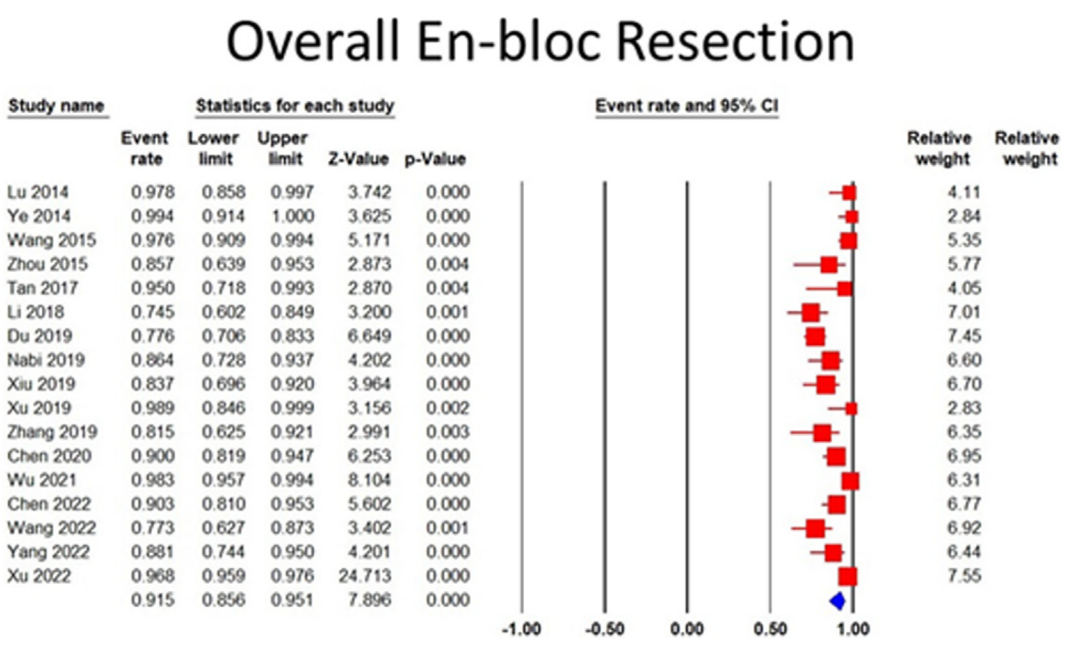

Figure 3. Forest plot for the pooled rate of overall en bloc resection.

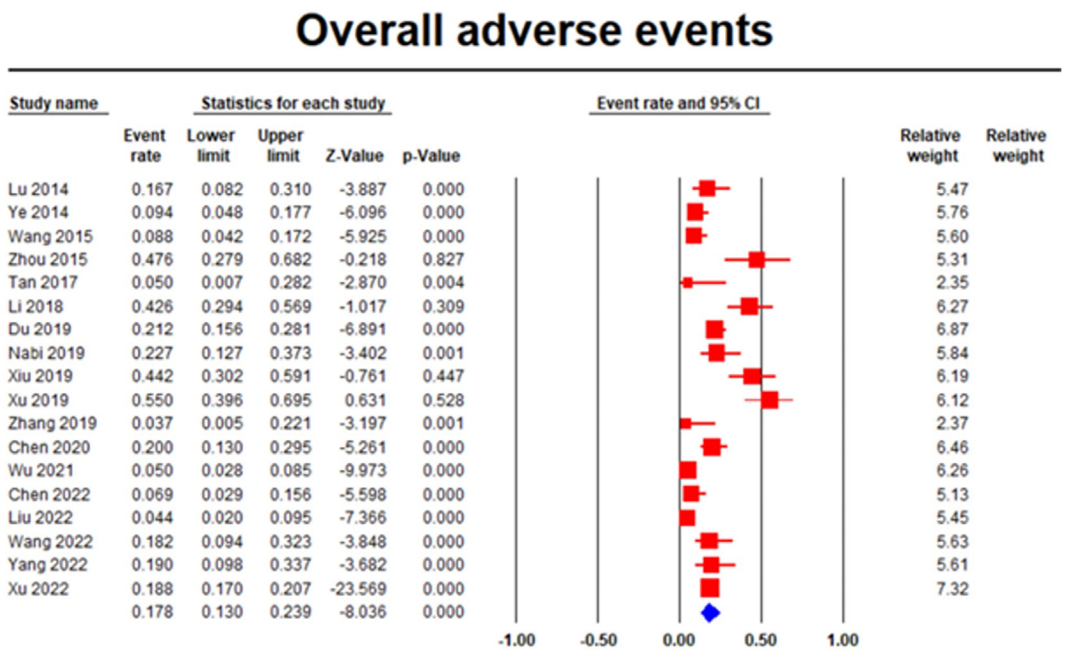

Figure 4. Forest plot for the pooled rate of overall adverse events.

Lesions arising from the MP layer throughout the upper GI tract

The pooled rates of R0 and en bloc resection for SETs arising from the MP layer throughout the upper GI tract were as follows: (1) R0 resection: 88.3% (95% CI, 74.3-95.1; $I^2 = 93$; $P = .000$); and (2) en bloc resection: 89.1% (95% CI, 81.8-93.8; $I^2 = 82$; $P = .00$).

Recurrence

The pooled rate of recurrence was estimated to be 2.3% (95% CI, 1.4-3.6; $I^2 = 0$; $P = .00$).

Validation of meta-analysis in results

Sensitivity analysis. To evaluate whether any of the included studies had a dominant effect, a leave-one-out

analysis was performed by excluding one study at a time and assessing its effect on the outcome. Li et al,[14] Xu et al,[27] and Zhou et al[28] each had a dominant effect on the overall rate of adverse events and the rate of mild adverse events. Xu et al[27] had a dominant effect on the pooled rate of gas-related adverse events without obvious perforation.

Publication bias. Based on funnel plots (Supplementary Figs. 1, 2, and 3, available online at www.igiejournal.org) and the Egger test, there was no publication bias for overall en bloc resection and adverse events; however, there was publication bias associated with overall R0 resection.

DISCUSSION

The current meta-analysis found that STER is a feasible and effective treatment modality for upper GI SETs, with high overall R0 and en bloc resection rates and a low rate of adverse events. Although still favorable, the R0 and en bloc rates may vary based on the region or the layer from which the SET is removed. Although there were prior systematic reviews and meta-analyses on STER,[2,10] this is the largest systematic review and meta-analysis to our knowledge to encompass all types of upper GI SETs treated with STER.

In our analysis, STER was shown to have high R0 and en bloc resection rates. Before the advent of STER, there was no existing endoscopic technique to retrieve sufficient tissue for definitive histologic examination and diagnosis.[29] Not only does STER function as a diagnostic tool by allowing procurement of adequate specimens, but it also allows removal of the lesion of concern with an intact capsule and tumor-free margins because the sites of mucosal incision and tumor resection are separate.[29,30] Furthermore, the tumors and the MP layer can be directly visualized through the submucosal channel, and hemorrhagic spots or mucosal defects, if present, can generally be detected and managed promptly.[2,10,31] There are, undoubtedly, certain challenges to achieving successful resection. It has been noted that large tumors (transverse diameter ≥35 mm), irregular shape, and extraluminal growth pattern can lead to the failure of STER and may necessitate other procedures such as piecemeal extraction or even surgery.[32,33]

The en bloc resection and R0 resection of the esophageal and gastric lesions were high; however, the en bloc resection rate of EGJ lesions was lower at 81.5%. The lower success rate can be explained by several factors. The anatomical location of the EGJ may impede visualization during the formation of the submucosal tunnel.[34] The proximity of the EGJ to the mediastinum increases the risk of perforation and may also impose technical challenges.

Similarly, SETs originating from the MP layer are deeper and can make endoscopic resection difficult, especially if they are closely attached to the serosa.[35] Hence, lower rates of R0 and en bloc resection were observed for the tumors in the MP layer.

The overall pooled rate of adverse events from this meta-analysis was 17.8% (95% CI, 13.0-23.9; $I^2 = 87$; $P = .00$). Because STER is not yet widely practiced, the lack of standardized definitions for adverse events of STER may contribute to the overestimation of adverse events.[29] When stratified using the ASGE lexicon, our analysis found that the pooled rates for mild, moderate, and severe adverse events were 15.4%, 3.4%, and 1.2%, respectively. In a compilation analysis of 1701 patients by Xu et al,[29] 18.8% of patients experienced adverse events. However, most (13.8%) were mild adverse events per the ASGE lexicon and resolved spontaneously; only 5.8% required additional treatment. Operation time >60 minutes, mucosal injury during the procedure, distance >6 cm from incision to tumor, and requirement for piecemeal resection have been reported as independent risk factors for major adverse events during STER. There was no mortality associated with STER in our analysis.

The pooled rate for perforation (3.4%) was higher than the previously reported rate from a RCT by Liu et al[36] (.9%). The inclusion of studies in which STER was used to remove tumors from the EGJ may have contributed to the higher rate of perforation. The low rate of bleeding can be explained by the fact that a hemorrhage can be detected and treated immediately given the direct visualization of the tumor and any surrounding vessels through the tunnel, and large vessels may have been prophylactically cauterized during the STER procedure.[26,31]

The lesion recurrence rate was low at 2.3%; the largest number of recurrent cases was 4.41% among a sample of 136 patients by Liu et al,[36] which focused on SETs in the esophageal MP layer. As discussed earlier, the deeper nature of the SETs in the MP layer can interfere with the success of the procedure. Although STER has an R0 resection rate of 92%, the recurrence rate was still low, even among tumors with a traditionally high rate of recurrence such as GISTs.[37] The average duration of follow-up in the included studies was 13.57 ± 7.03 months. It is possible that a higher recurrence rate may be detected with a longer follow-up period. The locations and types of SETs that resulted in recurrence were also not delineated in the studies included in the meta-analysis.

There are several limitations to the current study. First, because this was a systematic review and meta-analysis, we were not able to change or remove the confounding variables that may be present in the protocols of each study. Second, all studies that were included in the meta-analysis were observational studies except for one RCT. Third, because the follow-up period varied for different studies, the recurrence rate may not be accurate for the participants in some studies. It may also be worthwhile to investigate the locations and types of SETs with recurrence in future studies. Fourth, the definition of perforation varied across different studies. It is possible that the rate of perforation was overestimated given the nature of STER and the variations of definitions across different studies. Future studies with a standardized definition of perforation may be beneficial. Fifth, there was

evidence of publication bias in the pooled rate for overall R0 resection. Lastly, the included studies did not report on the diagnostic role of STER in previously undiagnosed SETs. It is true that FNA is an existing tool for diagnosis, especially in the setting of potential adverse events associated with STER and if the tumor is benign. However, as many as one-half of the specimens procured by FNA may be inadequate in differentiating SETs.[29] Further studies that investigate the role of STER in such circumstances may be beneficial.

In conclusion, our systematic review and meta-analysis showed that STER is an effective and safe therapeutic tool for the management of upper GI SETs with high rates of R0 and en bloc resection.

DISCLOSURE

All authors disclosed no financial relationships.

Abbreviations: ASGE, American Society for Gastrointestinal Endoscopy; CI, confidence interval; EGJ, esophagogastric junction; ESD, endoscopic submucosal dissection; GIST, GI stromal tumor; MP, muscularis propria; RCT, randomized controlled trial; SET, subepithelial tumor; STER, submucosal tunneling endoscopic resection.

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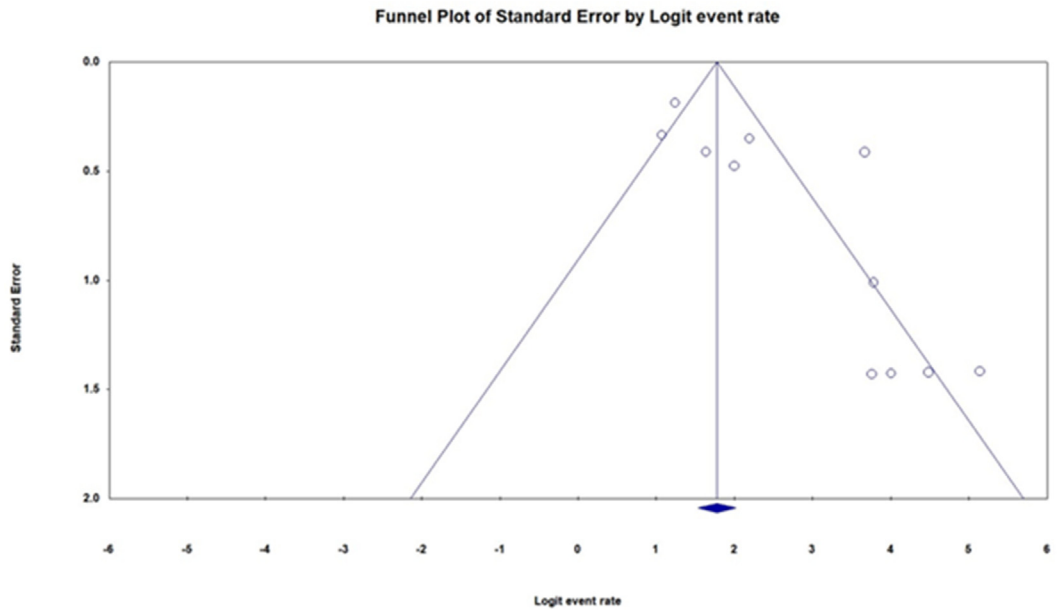
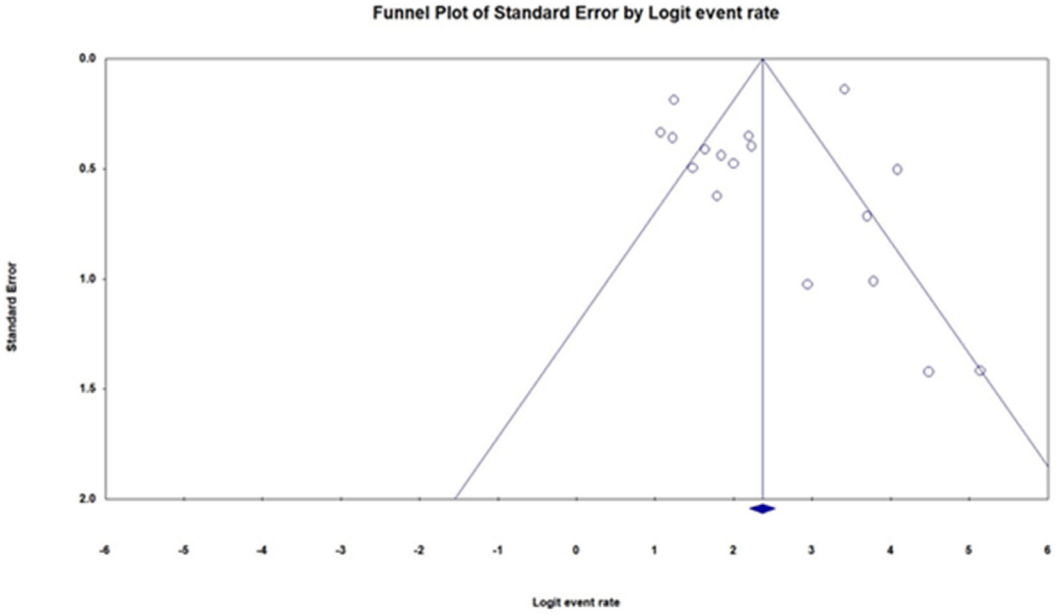
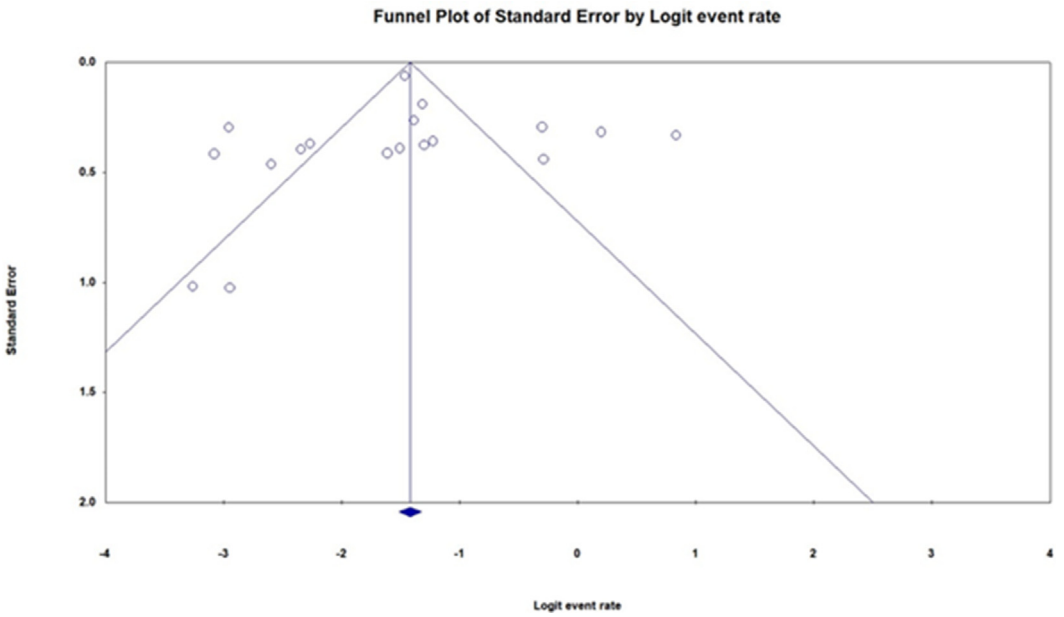


Supplementary Figure 1. Funnel plot that assesses the publication bias for overall R0 resection for upper GI SETs with STER.



Supplementary Figure 2. Funnel plot that assesses the publication bias for overall en-bloc resection for upper GI SETs with STER.



Supplementary Figure 3. Funnel plot that assesses the publication bias for overall adverse events for upper GI SETs with STER.